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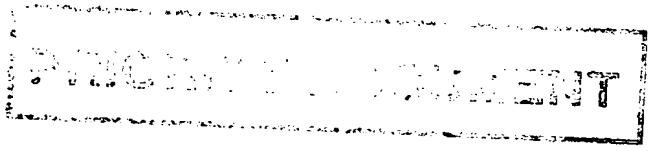
Patentanmeldung Nr. Patent application No. Demande de brevet n°

96201290.2



Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

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Page 2 de l'attestation

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Anmelder:
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Instant powder for the preparation of dispersions of reversed vesicles

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INSTANT POWDER FOR THE PREPARATION OF DISPERSIONS OF REVERSED VESICLES

The invention relates to an instant powder, which on reconstitution in an apolar vehicle, forms a dispersion of reversed vesicles, a method for the preparation of the said powder and compositions comprising the powder.

Vesicles in apolar vehicles were described in 1991 by H. Kunieda et al (J. Am. Chem. Soc. 113 (3) 1051-1052). The reversed vesicles, consisting essentially of the hydrophilic surfactant tetra-ethyleneglycol dodecyl ether in dodecane, were found to coalesce and revert back to a lamellar liquid crystalline phase over a period of hours to days, despite the addition of about 2.5 water molecules per ethyleneoxide-unit. International patent application WO 93/00069 disclosed dispersions of reversed vesicles in apolar vehicles, which vesicles were stable during a considerable period of time. The dispersions of vesicles disclosed therein were prepared by sonicating a mixture consisting of one or more surfactants, a lipophilic stabilising factor, optionally a hydrophilic stabilising factor and an apolar medium. Further publications on the same issue disclosed a preference for the use of straight chain hydrocarbon compounds as the apolar medium (H. Kunieda et al: Langmuir 1991 (7) 1915-1919, J. Coll. Interf. Sci 1991 (147) 286-288, J. Coll. Interf. Sci 1993 (156) 446-453). However, such dispersions have a very limited practical significance for product development in view of the very bad cosmetic and palatability properties of the said compounds and also because these compounds are not biodegradable.

On substituting the hydrocarbon compounds by biodegradable apolar compounds, such as glycerol tri-esters of higher saturated and unsaturated fatty acids having 10-30 carbon atoms and vegetable oils, in order to also improve the cosmetic and palatability properties, the yield of reversed vesicles, as assessed by polarised-light microscopy, is rather poor in the present inventors' experience.

Since dispersions of reversed vesicles have shown distinct advantages over those of vesicles in aqueous vehicles, among other things a high encapsulating capacity for both lipophilic and hydrophilic drugs and a high encapsulating efficiency for hydrophilic drugs, there has been a demand to find a way of improving the cosmetic and palatability properties of dispersions of reversed vesicles without adversely effecting the encapsulating capacity and efficiency thereof.

It is an object of the present invention to provide an instant powder, which on

reconstitution in an apolar vehicle forms a dispersion of reversed vesicles. The powder in admixture with one or more excipients may be incorporated in compositions.

A process for the preparation of the said instant powder by preparing a primary dispersion of reversed vesicles in a suitable apolar vehicle and subsequently removing the apolar vehicle preferably by evaporation is also provided.

It has now been found that by making a primary dispersion of reversed vesicles in a suitable apolar vehicle according to methods known in the art and subsequently removing the said apolar vehicle an instant powder is obtained, which on reconstitution in the same apolar vehicle reforms the dispersion of reversed vesicles. It has surprisingly been found that the same powder on reconstitution in another apolar vehicle also forms a secondary dispersion of reversed vesicles.

The present invention provides an instant powder, which on reconstitution in an apolar vehicle, forms a dispersion of reversed vesicles. The powder advantageously comprises a bio-active agent.

The powder is prepared by a process, which comprises the steps of:

- making a primary dispersion of reversed vesicles optionally containing a bio-active agent in a suitable apolar vehicle according to methods known in the art, such as disclosed in international patent application WO 93/00069, and
- subsequently removing the said apolar vehicle.

The primary dispersion of reversed vesicles can be made from a variety of surfactants, lipophilic stabilising factors and optionally hydrophilic stabilising factors as disclosed in international patent application WO 93/00069. Preferably a sucrose ester is used as the surfactant, cholesterol as the lipophilic stabilising factor and a small amount of water as the hydrophilic stabilising factor.

Removal of the apolar vehicle from the primary dispersion of reversed vesicles can be performed in several ways, such as by evaporation, centrifugation, filtration, lyophilisation etc. However, it is important that the bilayer structure of the vesicles will not be perturbed during the removal. There is a preference for evaporation techniques, in particular rotational evaporation and spray-drying. On using these processes it has appeared that the addition of excipients such as the so-called cryoprotectants used during lyophilisation processes is not necessary.

The apolar vehicle to be used for making the primary dispersion of reversed vesicles is a non-solvent for the reversed vesicles and/or the components, making up the vesicles,

including the bio-active agent, and is selected from compounds or mixtures thereof which are not biodegradable and have a relatively high vapour pressure, in particular below the temperature at which the vesicles melt. Examples of such apolar vehicles are volatile silicone oils such as Abil®K4 and isoalkanes, such as isoparaffines.

The powder, obtained as described above and in details in the appended examples, consists of a vesicular structure, as a consequence of which a bio-active agent, if included in the primary dispersion of reversed vesicles, remains encapsulated. It may together with one or more excipients be incorporated in compositions, encompassing another aspect of the invention. The excipients may be solid in the form of dry powders or granulates in order to make tablets, capsules etc. The excipients may also be liquid or semi-solid in order to prepare dispersions. The liquid may be a polar compound such as water, but is advantageously a biodegradable compound. It has been demonstrated that in this way it is possible to make dispersions of reversed vesicles in a biodegradable apolar compound in a high yield, as compared to those directly made in the biodegradable compound according to the methods known in the art. Examples of such biodegradable natural or synthetic compounds are fatty acids, such as oleic acid, vegetable oils, such as peanut-oil and sesame oil, and mono-, di- and triglycerides of saturated and unsaturated, straight-chain fatty acids with 12 to 30 carbon atoms such as lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid.

Whichever the way the powder according to the present invention is incorporated into a composition, it is clear that the bad cosmetic and palatability properties of the hydrocarbon apolar dispersion vehicle have been eliminated. Since the encapsulation efficiency of the reversed vesicles for bio-active agents is highly influenced by the choice of the apolar vehicle, it is a further advantage that the powder according to the present invention is obtained using an apolar vehicle, which is a non-solvent, also for the bio-active agent. On dispersion of the powder in another apolar solvent to form a secondary dispersion of reversed vesicles a high encapsulation efficiency of the bio-active agent has been found.

Although the foregoing invention has been described in some detail by way of illustration and example for purpose of clarity and understanding, it will be readily apparent to those of ordinary skill in the art in the light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and the scope of the appended claims.

The following examples further illustrate the invention.

EXAMPLE 1

44.375 g of a silicone oil (Abil®K4), 5 g of sucrose palmitate P1570 (a mixture of 70% mono-esterified and 30% di- and poly-esterified sucrose, as obtained from C.N. Schmidt B.V., Amsterdam, The Netherlands), 0.5 g of cholesterol and 0.125 g p-aminobenzoic acid (PABA) were weighed into a thermostated vessel at 90°C. The mixture was sonified at 97 watts output during 30 minutes using a Branson sonifier 250 (Branson Ultrasonics Corp. Danbury, U.S.A.) followed by cooling of the vessel with cooling water of 7.5°C during 15 minutes until room temperature was reached. During cooling the mixture was sonified at 97 watts output with a duty cycle of 50%. Crystallisation of the silicone oil at the wall of the vessel was prevented by also stirring the mixture using a magnetic bar during cooling.

1.1 Removal of apolar vehicle by rotational evaporation

50 ml of the dispersion of vesicles so obtained was transferred to a 250 ml round bottom flask. The silicone oil was allowed to evaporate using a Büchi Rotavap (Büchi Laboratoriums AG, Flawil, Switzerland), the waterbath being kept at 30°C. The rotational speed of the round bottom flask was set at five and the pressure was reduced to 0.1 bar. After evaporation was completed, the remaining film was gathered and milled in a mortar.

1.2 Removal of apolar vehicle by spray drying

50 ml of the dispersion of vesicles was transferred to a mini spray dryer (Büchi 190, Büchi Laboratoriums AG Flawil, Switzerland), operating conditions: airflow 500 NL/h, inlet temperature 67°C, outlet temperature 56°C.

EXAMPLE 2

890 g of the silicone oil Abil® K4, 100 g of sucrose palmitate P1570 and 10 g of cholesterol were weighed in a thermostated vessel kept at 70°C. The components were mixed for ten minutes using an Ultra Turrax high shear mixer. After this pre-homogenisation the mixture was transferred to a M110 T Microfluidiser device operated at a pressure of 9000 PSI (Microfluidics Corp., Newton, U.S.A.) and several cycles were passed. The microfluidiser was thermostated at 30°C using a Neslab Exacal Ex-410 device (Neslab, Newington, U.S.A.).

After the last cycle the dispersion was cooled using a Neslab Endocal RTE 220 flow-through cooling device (Neslab, Newington, U.S.A.), the temperature of the waterbath being set at 25°C.

2.1 Removal of apolar vehicle by rotational evaporation

50 ml of the dispersion of vesicles so obtained was transferred to a 250 ml round bottom flask. The silicone oil was allowed to evaporate using a Büchi Rotavap (Büchi Laboratoriums AG, Flawil, Switzerland), the waterbath being kept at 30°C. The rotational speed of the round bottom flask was set at five and the pressure was reduced to 0.1 bar. After evaporation was completed, the remaining film was gathered and milled in a mortar.

2.2 Removal of apolar vehicle by spray drying

50 ml of the dispersion of vesicles was transferred to a mini spray dryer (Büchi 190, Büchi Laboratoriums AG Flawil, Switzerland), operating conditions: airflow 500 NL/h, inlet temperature 67°C, outlet temperature 56°C.

EXAMPLE 3

1.125 g of the powdered product obtained according to example 1.1 and 8.875 g of an oil, selected from the group consisting of caprylic/capric triglyceride (Miglyol® 812N), peanut oil, castor oil, oleic acid and the volatile silicone oil Abil® K4, were weighed in a 20 ml sample vial. The mixture was stirred for 10 minutes at 150 rpm using a magnetic stirrer. The presence of reversed vesicles in the dispersions as so-called Maltese crosses was assessed by polarised light microscopy (Olympus® BH2 Tokyo Japan) immediately after preparation and after storage of the dispersions for 2 weeks at room temperature. The results have been listed in table 1.

Table 1

powder dispersed in	appearance
Miglyol® 812N	reversed vesicles and a lot of agglomerates of reversed vesicles
Peanut-oil	reversed vesicles and a lot of agglomerates of reversed vesicles
Castor oil	reversed vesicles and a lot of agglomerates of reversed vesicles
Oleic acid	reversed vesicles and some agglomerates of reversed vesicles
Abil® K4	reversed vesicles and a lot of agglomerates of reversed vesicles

No change in the appearance was observed after storage during two weeks at room temperature.

EXAMPLE 4

1.125 g of the powdered product obtained according to example 1.1 and 8.875 g of an oil, selected from the group consisting of caprylic/capric triglyceride (Miglyol® 812N), peanut oil, castor oil and the volatile silicone oil Abil® K4, were weighed in a 20 ml sample vial. The mixture was stirred for 10 minutes at 150 rpm using a magnetic stirrer.

Directly after preparation the encapsulation efficiency of PABA, defined as the percentage PABA encapsulated per gram of reversed vesicles dispersion, was calculated by means of the formula:

$EF = [1 - (f*FP/TP)]* 100\%$

wherein: f = the weight fraction of non-encapsulated apolar vehicle

FP = the concentration (mg/g) of PABA dissolved in the non-encapsulated apolar vehicle

TP = the concentration (mg/g) of PABA dissolved in the dispersion of reversed vesicles in the apolar vehicle.

The results have been listed in table 2.

Table 2

Powder dispersed in:	Encapsulation efficiency (%) mean ± SD (n=3)
Miglyol® 812N	71.8 ± 14.2
peanut oil	71.2 ± 0.9
castor oil	57.9 ± 0.8
Abil® K4	98.5 ± 0.1

EXAMPLE 5

A dispersion of reversed vesicles in an apolar medium, which is caprylic/capric triglyceride (Miglyol® 812N), peanut oil, castor oil, oleic acid and the silicone oil Abil®K4 was made according to the method of example 1.

The appearance of the dispersions was assessed by means of a polarised-light microscope as described in example 3, immediately after preparation and after storage of the dispersions for two weeks at room temperature. The results have been listed in table 3.

Table 3

dispersion of reversed vesicles directly prepared in	appearance
Miglyol® 812N	some giant reversed vesicles and a lot of non-vesicular material
Peanut-oil	some reversed vesicles, some PABA crystals and a lot of non-vesicular material
Castor oil	non-vesicular material only
Oleic acid	non-vesicular material only
Abil® K4	reversed vesicles only

No change in the appearance was observed after storage during two weeks at room temperature.

The encapsulation efficiency of PABA was not determined, due to the lack of (sufficient) vesicular material.

CLAIMS

1. Instant powder which on reconstitution in an apolar vehicle forms a dispersion of reversed vesicles.

2. Instant powder according to claim 1, characterised in that it contains a bio-active agent.

3. Process for the preparation of the instant powder according to claim 1 or 2 comprising making a primary dispersion of reversed vesicles optionally containing a bio-active agent in an apolar vehicle according to methods known in the art, characterised in that the apolar vehicle is subsequently removed.

4. Process according to claim 3, characterised in that the apolar vehicle is removed by evaporation techniques.

5. Process according to claim 3 or 4, characterised in that a volatile silicone oil is used as the apolar vehicle.

6. Composition comprising the instant powder according to claim 1 or 2.

7. Use of the instant powder according to claim 1 or 2 for the preparation of a dispersion of reversed vesicles in a vehicle consisting of one or more biodegradable excipients.

ABSTRACT

An instant powder, which on reconstitution in an apolar vehicle forms a dispersion of reversed vesicles, optionally containing an active ingredient, can in admixture with one or more excipients, preferably biodegradable oils, be incorporated in compositions.

The process for the preparation of the said instant powder involves the preparation of a primary dispersion of reversed vesicles in a suitable apolar vehicle, which vehicle is subsequently removed.